Absorption

Introduction

Absorption refers specifically to a drug's getting from the air (outside the person) into the plasma.

Regardless of whether it's a pill swallowed, an injection into the bloodstream, or a dissolvable capsule inserted into the rectum, the whole point of "giving a drug" is to get that drug into the bloodstream. Direct inoculation of the drug into the target organ isn't practically effective most of the time (epidural anesthesia and intrathecal chemotherapy are exceptions). We want the seizure medication in the person's brain, and we want the hepatitis C treatment in the liver, and we don't want those treatments anywhere else. But practically we introduce a drug into the plasma and the heart pumps the drug through the body (see #3: *Distribution*). Certain medications (e.g., topical creams) are meant to act locally, and don't need to be absorbed. But for most drugs, and for the entire discussion in this lesson, we are assuming that absorption means getting the drug from outside the body **into the plasma**.

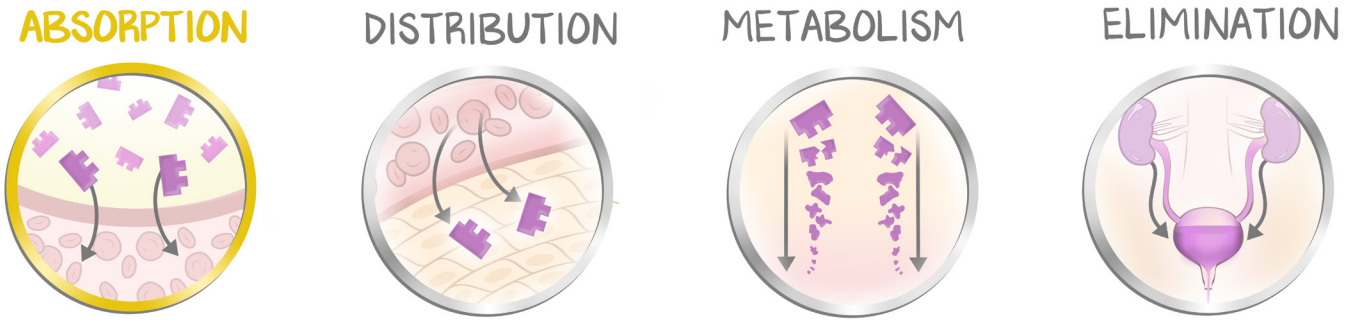

Figure 2.1: Pharmacokinetic Map, Absorption
In this lesson we are specifically speaking about the process of absorption, getting the drug from outside the body into the plasma.

We'll introduce some drug curves and then discuss the factors that alter absorption. In the introductory lesson, we introduced the concepts of diffusion, solubility, ionization, and transport mechanisms. Those are all true here and will continue to be true—at least in the form of the diffusion equation as it pertains to drugs. But now we introduce the concept of route. **Route of administration** has a huge impact on how much drug will reach the plasma and in how much time.

Understanding Dose-Administration Curves

The curve in Figure 2.2 represents what happens to the **plasma concentration** of a drug after a single dose of medicine has been given. This curve will change based on any of the parameters discussed in #1: *General Principles* and based on the **route of administration** (more on this soon). We will use it to define some pharmacokinetic parameters. Refer to it as you progress through the next few paragraphs.

The nomenclature gets frustrating. Absorption is a pharmacokinetic term that means get-drug-into-plasma, and elimination is a pharmacokinetic term that means get-drug-out-of-the-body. The **time period of absorption** is defined by the curve with a **positive slope**, whereas the **time period of elimination** is defined by the curve with a **negative slope**. During the periods of both absorption and elimination, the processes of absorption, distribution, metabolism, and elimination are occurring. The word "absorption" is used for the action of the drug's being absorbed, and to name the time period of net absorption on the graph. Likewise, the word "elimination" is used for the action of the drug's being eliminated from the body and to name the time period of net elimination on the graph. Don't get jammed up by the terminology. Let's focus only on the graph for now.

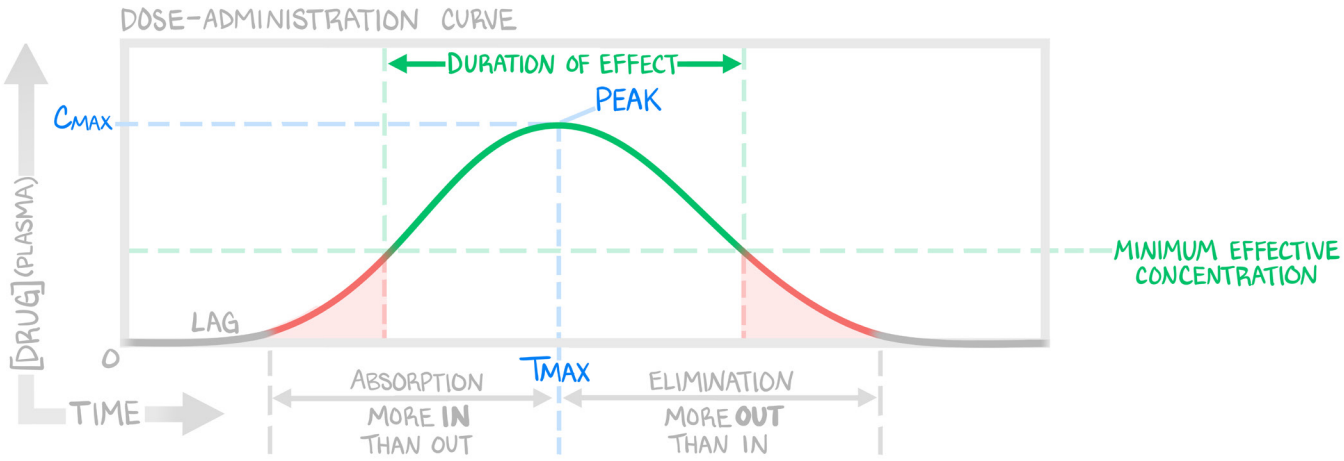

Figure 2.2: Dose-Administration Curve
This is specifically an example of an orally administered pill that has the initial lag, the rise of absorption below the minimum effective concentration, the peak concentration of drug, then the fall as elimination wins over absorption, past the minimum effective concentration, back to undetectable levels.

When the curve has a positive slope, during the time period of absorption, the **process of absorption is winning** (more in than out). When the curve has a negative slope, during the time period of elimination, the **processes of metabolism and elimination are winning** (more out than in).

The curve is set up with the **concentration of drug in plasma** on the y-axis, and **time** on the x-axis. Over time, the drug concentration will change based on the balance of in vs. out. I think this is easiest to understand when we try to make it NOT generalizable, when we talk as if the route were oral: swallowing a pill.

The pill is swallowed and the timer is started. There is a **lag** between administration (swallowing) and measurable plasma levels (the sugar coating on the pill has to dissolve, then the drug can start getting through the gut wall). The **time period of absorption** is from the moment the drug is detectable until the **peak concentration**. The peak concentration is named $\mathbf{C_{max}}$. The time point at which C_{max} is reached is called $\mathbf{T_{max}}$. These will be useful for assessing half-life in #5: *Elimination*. The **time period called elimination** is from the moment the drug is at C_{max} to the moment it becomes undetectable.

Effective Concentration and Duration of Action

Just because a drug is present in the plasma, just because plasma concentration is rising, just because the drug is measurable in a serum sample, doesn't mean the drug is actually working. For every drug there's a **minimum effective concentration** that must be reached before the drug does anything. The **duration of action** of a single dose is defined by the time between when it reaches the minimum effective concentration on the way up, and the time it reaches the minimum effective concentration on the way down. This is different than the amount of time a drug is in you, and is different than half-life. This is also different from the patient's subjective experience.

Some drugs work the same way just above minimum effective concentration as they do at a concentration much higher than the minimum effective concentration. β-Lactam antibiotics are most effective simply by being "over the line." The more time spent above minimum effective concentration, the better than antibiotic kills the infection. In this case, going higher serves only to risk toxic side effects.

But other drugs may work differently at different concentrations in plasma. Take the drug alcohol for an example—let's explore what happens when I take bigger and bigger doses, effectively increasing the

plasma concentration in my blood. I take one shot of tequila and I don't feel anything—the alcohol never reaches minimum "effective" concentration. I take four shots of tequila in an hour and it's a party—effective concentration achieved. I take eight shots of tequila at once and I don't make it to hour 2—minimum effective concentration achieved and exceeded.

This next example is going to take into account lag, absorption, elimination, duration of action, and patient subjective experience all at once. More seriously, consider a patient in pain. When they take the pain pill, there's a lag. They're still in pain. Then the medication starts to rise in their blood. They feel only pain, without relief, until the minimum effective concentration is reached. They still feel pain, but it gets to be less and less as the drug concentration rises higher and higher above the minimum effective concentration. The concentration peaks, then begins to fade, the pain gradually returning as the drug gradually wears off. If they wait for the pain medication's concentration to go to 0, they will experience no relief (or, maximal pain) from the time the medication concentration hits the minimum effective concentration, through the elimination of the drug, through the lag period, and through the next rise of concentration to minimum effective concentration. THEN, they will experience only the minimal amount of relief as the drug concentration rises. Best not to wait for maximal pain before the next dose.

Barriers to Absorption

Regardless of the route used, there's going to be some combination of barriers to absorption (read, as you know already, **barriers to diffusion**). Routes vary in the distance the drug must travel to get into the bloodstream and how many compartments the drug must cross before getting into the bloodstream. In addition, for those routes that involve the portal circulation, drugs also succumb to first-pass metabolism.

First-pass metabolism refers to the fact that any drug absorbed anywhere from the stomach to the promimal rectum is absorbed into portal circulation. All of the portal circulation goes to the liver before getting to the peripheral veins. Which means that the liver gets a chance to process that drug (see Pharmacology #4: *Metabolism/Biotransformation*) before any of it reaches the circulation.

Any route that does not involve the stomach to the colon avoids first-pass metabolism. These routes of administration include sublingual (under the tongue) and per rectum—both drain to caval circulation and bypass the liver. Any route of administration that avoids the GI tract altogether also has the same effect. In fact, some drugs have such a high first-pass metabolism that they simply cannot be given orally—**nitroglycerin** must be given as a transdermal patch or sublingually, and **lidocaine** for cardiac arrhythmias can be given only intravenously.

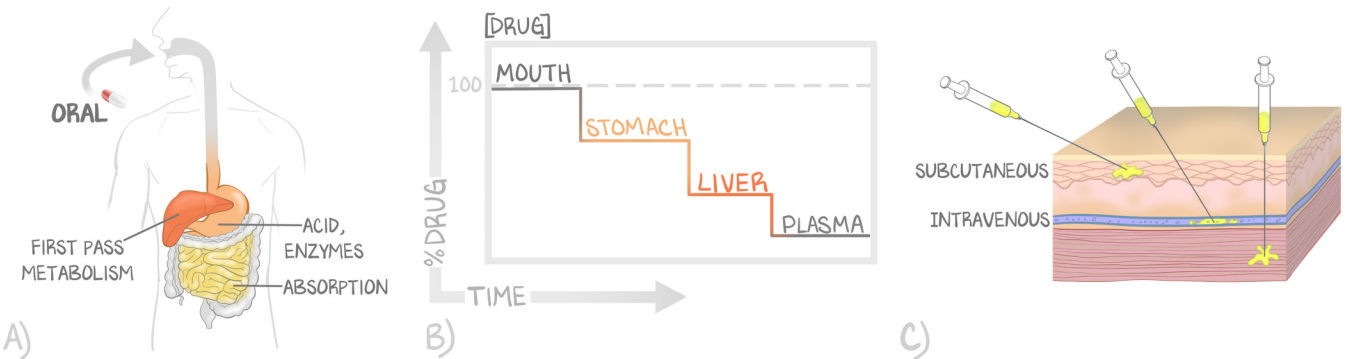

Figure 2.3: Barriers to Absorption
(a) The first barriers to oral absorption are the multiple compartments of the GI tract with varying pH and digestive enzymes. (b) The representative (not literal) loss of drug efficacy caused by initial ingestion, destruction by stomach acid and digestive enzymes, then first-pass metabolism, demonstrating that very little of an oral dose reaches plasma. (c) Based on the route of administration, there may be a larger distance to diffuse between intravenous, intramuscular, and subcutaneous.

Other barriers to absorption are the same barriers to diffusion we talked about in #1: *General Principles*. Drugs must diffuse into the circulation. And since these drugs are passing through cells—either the enterocytes of the gut or the endothelial cells of the blood vessels—the only thing the drug has to rely on is the diffusion equation (no human cell has developed the genetic code to transport a pharmaceutical across the plasma membrane into a cell).

Route of Administration

There are many routes of administration. Those that involve the GI tract are said to be **enteral**, whereas those that don't involve the GI tract are **parenteral**. Each route of administration has its benefits and its risks, and not every drug can be given through every route. So we will be speaking generally about the different routes, but then as you study individual drugs, you will need to know which routes are effective, which are dangerous, and which just won't work. Let's start generally.

Parenteral routes include intravenous, intramuscular, subcutaneous, transdermal, and inhaled. **Enteral routes** include sublingual, oral, and per rectum. The various routes differ in convenience of administration (pills are easier to swallow every day than a needle is to inject in a vein) and how well they escape or succumb to the barriers of absorption—either diffusion or first-pass metabolism.

Let's start with parenteral, because intravenous is the "best" route of administration.

Intravenous administration (puncture of a vein and direct inoculation of the drug into the caval system) bypasses all barriers of absorption and escapes first-pass metabolism. The definition of absorption was to get the drug from outside the body into the plasma. Intravenous administration starts the drug in the plasma, which means that **100% of the drug** is already in the plasma. IV administration starts at C_{max}, so everything that follows it is the elimination phase (the negative part of the curve that encompasses metabolism and elimination).

Intramuscular administration (puncture of the skin to deep muscle) is similar to intravenous, except you don't need venous access. This means there is inherently an escape of first-pass metabolism. But there is a diffusion barrier. The distance from inoculation in the muscle to the vasculature is greater than 0, so the time it takes to diffuse will mean that intramuscular isn't as good as intravenous. Some medications meant to be intravenous are caustic in tissue. Some medications can be given IM when no IV line exists—morphine for pain, benzodiazepines for seizures.

Subcutaneous administration (puncture of the skin into fat but not deeper into muscle) is similar to intramuscular, except that being in the fat means there is an even greater diffusion barrier to pass than intramuscular. This can have its advantages. Insulin, for example, is injected into the SubQ space. Because the diffusion takes time, a single administration can cover several hours of glucose. Although IV would be faster, the IV dose would wear off faster, and the convenience of a very small needle into the SubQ space is better than a long large needle puncturing the vein, at every meal.

Transdermal route is restricted to a small number of medications. Most medications cannot diffuse across the epithelium. But for those that can there is the added benefit of convenience—place a patch and the patch does the rest. A sustained delivery of medication is achieved from the patch, and some patches only need to be changed every few days, or even weeks. This is best when there is an issue with compliance. For example, clonidine is taken three times a day for hypertension, and a missed dose causes rebound hypertension. Rather than miss a dose, a clonidine patch can be applied every three days—fewer missed doses. Transdermal is also used when infrequent dosing is desired such (the nicotine patch is changed every week).

Inhalation is tricky—though it would seem an obvious route of administration. After all, the lungs are designed for maximal diffusion of the "drug" oxygen. Lots of surface area, small diffusion barrier, all the things that we used in the last lesson to enhance absorption. And it is delivered to the left ventricle, so it will be readily distributed throughout the body. But when it comes to actual medications, only a few drugs have a chemical composition that renders them good candidates for inhalation. To be sure, it's a real thing—smoking crack cocaine gets you higher faster than ingesting it, anesthetic gases like halothane cause rapid sedation—but most drugs just don't work through inhalation. Inhaled insulin (so diabetics can stop stabbing themselves with insulin-filled needles every meal) has been a pipe dream for 40 years. You should learn inhalation as a special case, know which medications are administered this way, and leave it out of any spectrum or memory tool.

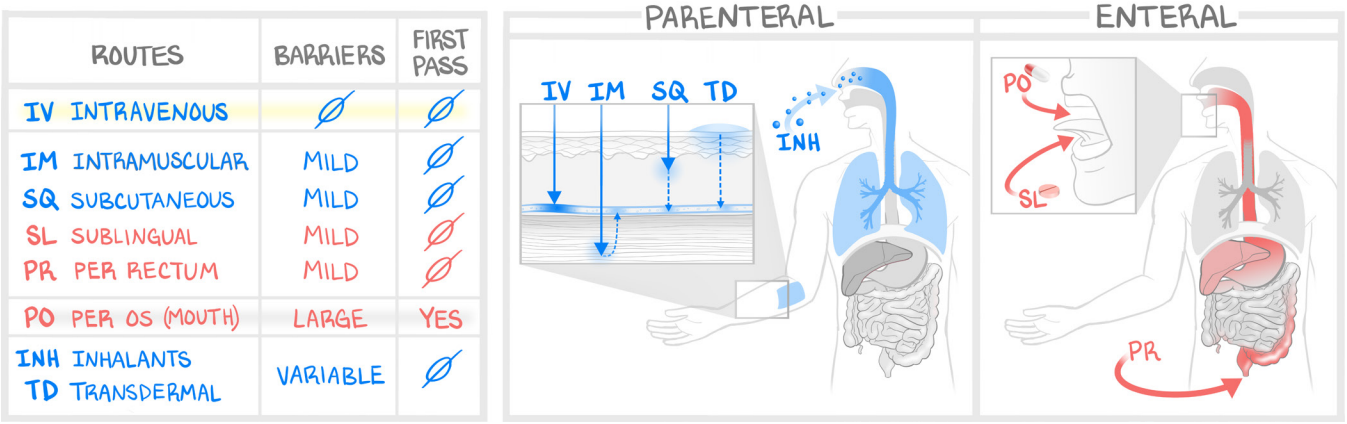

Figure 2.4: Routes of Administration
IV is the best, PO has the largest barrier, and inhalation and transdermal are variable. The enteral routes, PO, SL, PR are shown highlighted in red. The parenteral routes are highlighted in blue, comparing their relative barriers to diffusion-distance.

Changing gears to enteral routes.

Oral is the most convenient for the patient—taking a pill, swallowing it like we ingest everything else—but has the most barriers to absorption of any route. When a pill is swallowed, it encounters the stomach. The acid destroys some of the drug; the pH may ionize it, trapping it in the stomach; enzymes of digestion may degrade the drug. After getting into the intestines, the surviving drug must then cross the gut endothelium, where it's delivered to the **portal circulation**. Because all of the portal circulation goes through the liver, the liver gets a shot at **first-pass metabolism**: the liver starts to metabolate the drug even before it has hit the circulating bloodstream. Oral is the most common way to administer medications, but some medications either cannot be absorbed by the gut or the drug is metabolized by the liver and never enters the portal circulation.

Sublingual is an enteric route because it involves the mouth. Most medications cannot be absorbed this way. Specialized formulations of oral medications, designated "ODT" (oral dissolvable tablet), have been made, but nitroglycerin is the quintessential sublingual medication. A tablet of nitro is placed under the tongue or a spray is sprayed under the tongue. The highly vascular tongue absorbs the medication into systemic circulation, bypassing first-pass metabolism.

Rectal administration is also an enteric route. Like the mouth, the distal end of the rectum drains into the system circulation. More oral medications can be absorbed through the rectum than sublingually, but the inconvenience of this route of administration limits its use. Most often it is used when a medication that must be given orally cannot be, as in a stroke patient who must receive aspirin but who cannot swallow because of that stroke.

Bioavailability

Intravenous gets all of the drug into the plasma—perfect absorption. In Figure 2.2 we compare the curve of intravenous (C_{max} at time 0, then monitor elimination) to the curve of any other route of administration. From that, we determine a drug route's bioavailability. **Bioavailability** is a characteristic of the drug, which is defined as **the percentage of drug that reaches circulation relative to the intravenous dose**. It's determined through studies on many patients, on a **population**. It's calculated by determining the area under the curve of the IV dose, divided by the area under the curve of the PO dose. Since I didn't do very well in calculus and calculating the area under a curve is something I never want to do again, let's say it differently:

Bioavailability is the relative dose required via a given route of administration to get the same effect as an IV dose. "Same effect" doesn't mean an equal C_{max}, or equal duration or time to onset of action, etc. It's a cumulative concept of everything just listed. The "area under the curve" takes into account all the features of absorption and elimination. IV will have the "highest high" and the "fastest onset of action" by definition, being intravenous. But bioavailability is about the cumulative effect of a dose.

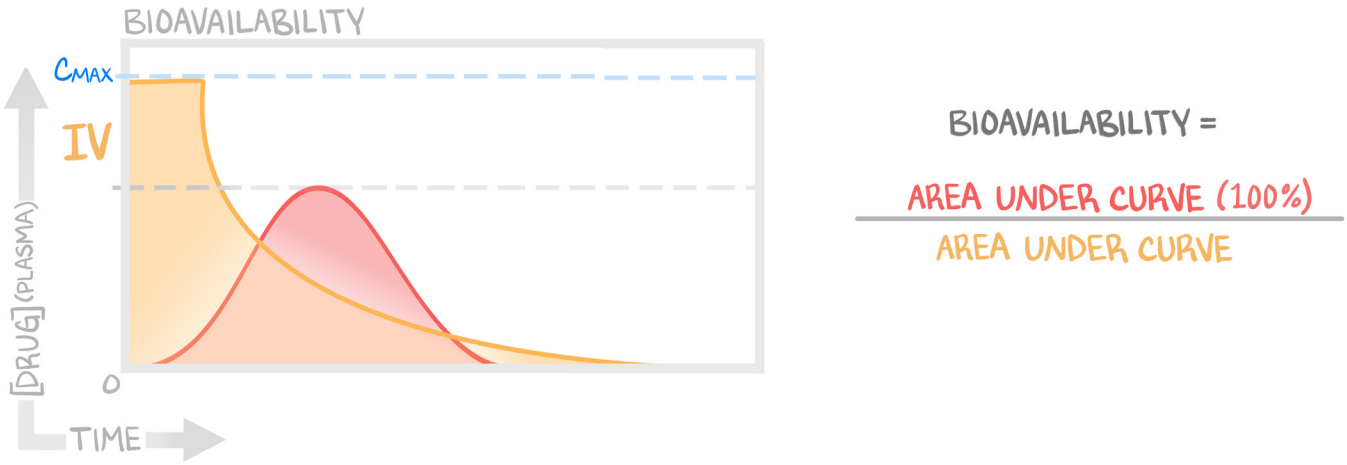

Figure 2.5: Bioavailability
Comparing the area under the intravenous dose curve (C_{max} instantly, so only elimination) with the area under the curve of another route will give a mathematical comparison. The bioavailability is expressed as a percent of the IV dose.

Examples:

Ciprofloxacin has an oral bioavailability of 100%. This means that the oral dose of ciprofloxacin has the same effect as an intravenous dose of ciprofloxacin. So if you have a Gram-negative rod bacteremia sensitive to ciprofloxacin and some other antibiotic, ciprofloxacin makes the most sense to give—and giving oral ciprofloxacin is the same as giving it IV . . . and "IV is best."

But a patient with chronic pain won't get the same relief from an oral preparation of morphine as he will from an intravenous dose. Morphine has a much lower bioavailability than 100%. Morphine 4 mg intravenously is a hefty dose that will sedate everyone except the most tolerant patients, whereas morphine 15 mg orally is considered the smallest dose effective for the oral route.

The problem goes beyond that. Because for the individual in front of us, not only is there an **inherent bioavailability**, but also whatever the patient is doing to herself. Because the food we eat, the transit time of the GI system, the acidity of the gut, and other things change, the patient in front of us will have a variable absorption. What you should know, for sure, is that, in general, the **more parenteral** the administration, the faster and better the absorption.